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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,184	09/24/2004	Alexander D Slowey	57666US005	7403

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EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
06/30/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/509,184	SLOWEY ET AL.	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-14 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5-14, and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 5-14 and 17 are pending. Applicants previously cancelled claims 15-16. Applicants newly cancelled claims 2-4. Applicants amended claim 1. Receipt and consideration of Applicants' claim amendments and remarks/arguments are acknowledged. All rejections/objections not explicitly maintained in the instant office action have been withdrawn per Applicants' claim amendments and/or persuasive arguments.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5-14 and 17 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Oliver et al. (U.S. Patent No. 6,054,488) (IDS reference) in view of, Cutie (U.S. Patent No. 6,129,905) (IDS reference), Gavin et al. (WO 01/78740), and Ashurst et al. (U.S. Patent No. 6,131,566) (of record).

Applicant Claims

Applicants claim (1) a dispenser containing a pharmaceutical formulation comprising (a) formoterol fumarate dihydrate, (b) mometasone furoate (c) a propellant selected from 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, or mixtures thereof, and (d) a bulking agent having a mass median diameter of less than one micron, wherein the interior surface of the aerosol vial is coated with a fluorocarbon polymer and (2) a method of making the formulation recited in claim 1 comprising (a) forming a slurry of the bulking agent with another formulation component, (b) homogenizing the slurry, and (c) combining the slurry with the remaining formulation components.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Oliver teaches pharmaceutical suspension formulations comprising (i) 0**.0025% to 0.1% w/w formoterol or an acid addition salt thereof**, (ii) 0.1-5.0% w/w ethanol, (iii) **a propellant comprising HFA 134a (i.e. 1,1,1,2-tetrafluoroethane), HFA 227 (i.e. 1,1,1,2,3,3,3-heptafluoroethane), or mixtures thereof**, (iv) **a micronized bulking agent** (e.g. lactose) in a

weight ratio of formoterol to bulking agent of from 1:3 to 1:100, and (v) a surfactant (title; abstract; col. 3, lines 5-42 and 45-59; and claims 1-19). Oliver teaches that the **micronized bulking agent may prevent the drug from creaming** by co-flocculating the drug (col. 3, lines 55-59). **Suitable bulking agents include lactose, DL-alanine, ascorbic acid, glucose, D(+)-trehalose dihydrate**, etc. (Id. at lines 52-55).

Formoterol is art-recognized as a long-acting beta-2 agonist that is suitable for metered dose inhaler formulations, is highly potent, and requires a considerably lower dosage than other drugs (col. 2, lines 51-55). The formulations are made in a glove box purged with dried air by (i) adding a small quantity of propellant to a pre-chilled stainless steel vessel, (ii) adding pre-chilled ethanol, (iii) **slowly dispersing pre-chilled drug and/or bulking agent into the propellant/ethanol mixture to obtain a concentrate** (i.e. preparing a slurry), (iv) **adding a homogenizer to the concentrate vessel**, (v) adding the concentrate to bulk propellant in a batching vessel, (vi) dispensing the formulation **into pre-chilled aluminum cans**, which are immediately sealed with a metering valve on each can (col. 4, lines 19-53). Oliver's method thus makes a dispenser fitted with a valve. The aluminum cans used in Oliver's method fairly read on vials.

Cutie teaches aerosol formulations containing (i) **a sugar as a dispersant/diluent (i.e. bulking agent), (ii) a propellant (e.g. HFA 134a and/or HFA 227), and a suspended drug (e.g. salmeterol xinafoate, beclomethasone, etc.)** (title; abstract; col. 3, lines 20-42; col. 4, lines 25-35; and claims 1-19). Mixtures of two or more drugs may be used (col. 4, lines 35-37). The sugar diluent/dispersant aids the incorporation of the dispersion in hydrocarbon and HFA propellants and provides many benefits, such as (i) facilitating the dispersion of the drug(s)

and/or excipients, (ii) stabilizing the formulations, either physically, chemically, or both, (iii) facilitating transfer of the drug, (iv) facilitating the drug's micronization and/or deaggregation in vitro, (v) acting as a respiratory sensitizer or desensitizer of drug surface interactions at topical and/or mucosal surfaces, and (vi) acting as a density modifier (col. 4, lines 15-24). **The particle size of the sugar should be no greater than 10 microns, preferably less than 5 microns in diameter, most preferably substantially all of the particles should be less than about 2 microns in diameter and there is no lower limit on the particle size** (col. 4, lines 62-67 and col. 5, lines 1-4).

Gavin teaches pharmaceutical aerosols suspension formulations comprising (i) an **anti-inflammatory steroid (i.e. mometasone furoate) or salt, solvate, or derivative thereof, (ii) a bronchodilator (i.e. salmeterol xinafoate) or salt, solvate, or derivative thereof, and (iii) a propellant (e.g. 1,1,1,2-tetrafluoroethane)**, which are suitable for the **treatment of respiratory disorders, such as asthma and COPD** (title; abstract; pg. 1, lines 1-6, 17-20, 25-34; pg. 2, line 30 through pg. 3, line 18; pg. 4, lines 4-7; Examples 1-3: pg. 8, lines 1-20; and claims 1-7). The formulations may comprise other therapeutic agents, such as other anti-inflammatories (e.g. fluticasone propionate, beclomethasone dipropionate, etc.), beta-2 adrenoreceptor agonists (i.e. betamimetic bronchodilators, such as, **formoterol**, etc.), anti-cholinergics, (e.g. tiotropium), etc. (pg. 5, line 33 through pg. 6, line 6). In Gavin's example 1, the exemplified formulation comprises 0.048% w/w salmeterol (i.e. a bronchodilator), 0.269% w/w mometasone furoate, and remainder 1,1,1,2-tetrafluoroethane.

Ashurst teaches that in some aerosol suspension formulations drugs (e.g. albuterol) adhere to the inner surfaces (e.g. can, valves, caps) of metered dose inhalers (col. 1, lines 51-58).

The problem of drug adhesion is especially acute in hydrofluoroalkane propellant (e.g. P134a and P227, which are synonyms of HFA 134a and HFA 227) systems (Id. at 55-58). **The problem of drug adhesion is resolved by coating of the interior can surfaces with a fluorocarbon polymer** (col. 1, lines 59-63; abstract; and claims 1, 37, and 47). Suitable fluorocarbon polymers and MDI can materials are disclosed by Ashurst at col. 4, line 32 through col. 5, line 29).

Regarding **formoterol fumarate dihydrate**, Applicants admit in paragraph [0006] of the specification of the instant application that **this salt hydrate of formoterol is well-known, such as in WO 01/78744**.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Oliver lacks the teaching of specific bulking agent particle size, formulations comprising mometasone in combination with a bronchodilator, and a dispenser having its interior surfaces coated with a fluorocarbon polymer. These deficiencies are cured by the teachings of Cutie, Gavin, and Ashurst, respectively.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have prima facie obvious at the time of the instant invention to utilize a bulking agent having a particle size of less than one micron, because both Cutie teaches that sugar bulking agents having a particle size of about 2 microns or less are suitable for ensuring the stability of pharmaceutical aerosol formulations comprising propellants, such as

hydrofluorocarbons. An ordinary skilled artisan would have been motivated to utilize the particle sizes taught as being suitable by Cutie for the bulking agent in Oliver's formulations, because said particle sizes are taught as being suitable to obtain formulations that benefit from the benefits of the inclusion of a sugar bulking agent (e.g. greater formulation physical and chemical stability). An ordinary skilled artisan would have had a reasonable expectation of successfully incorporating micronized bulking agents into Oliver's formulations, because Oliver teaches that the invented formulations require micronized bulking agent and Cutie teaches bulking agent particle sizes that promote the stability of pharmaceutical aerosol suspension formulation stability.

It would have prima facie obvious at the time of the instant invention to combine formoterol with mometasone, because both compounds are art-recognized as being suitable for the treatment of respiratory diseases such as asthma and COPD (Gavin). It is generally considered *prima facie* obvious to combine two compounds each of which is taught by the prior art to be useful for the same purpose, such as the treatment of asthma, in order to form a composition which is to be used for the very same purpose. The idea for combining them flows logically from their having been used individually in the prior art. See *In re Kerkhoven*, 626, F.2d 848, 205 USPQ 1069 (CCPA 1980). It is also noted that the combined prior art teaches/suggests the combination of two or more drugs (Gavin/Cutie). Thus, an ordinary skilled artisan would have had a reasonable expectation of successfully preparing aerosol suspension formulations comprising a mixture of formoterol and mometasone.

It would have prima facie obvious at the time of the instant invention to utilize a vial, such as an aluminum can, with its interior surfaces coated with a fluorocarbon propellant,

because the prior art recognizes that pharmaceutical suspension formulations utilizing hydrofluorocarbon propellants are acutely susceptible to problems of drug adhesion to the inner surfaces of metered dose inhalers (e.g. can/vial surfaces, cap, valve surfaces, etc.) and the art recognizes that coating the inner surfaces of a MDI with fluorocarbon polymers is a means to solve the art-recognized problem (Ashurst). An ordinary skilled artisan would thus have been motivated to coat the inner surfaces of a dispersing container (i.e. a MDI) with fluorocarbon polymers to reduce or prevent problems with drug adhesion and would have had a reasonable expectation of success, because the coating of the inner surfaces of MDI containers with fluorocarbon polymers is an art-recognized solution to the problem of drug adhesion in suspension aerosol hydrofluorocarbon propellant-based formulations.

Regarding claim 17, Oliver teaches the preparation of a slurry, homogenization of the slurry, and addition of the remaining formulation components. It is noted that the steps taught by Oliver are not in the same order as the steps recited in Applicants' claim 17. It is the Examiner's position that absent a showing of the criticality of the steps recited in Applicants' claim 17, it is prima facie obvious to modify the order of steps of a method. It is noted that Applicants' state that their formulations exhibited surprising little settling (i.e. creaming). This result is not considered surprising or unexpected, because the prior art (e.g. Cutie) recognized that the inclusion of sugar bulking agents having a particle size of less than about 2 microns enhanced suspension formulation stability (e.g. creaming was prevented and/or minimized). Specifically, regarding the bulking agent particle size recited in Applicants' claims, it is noted that the bulking agent particle size taught by the prior art substantially overlaps with the Applicants' recited bulking agent particle size. A prima facie case of obviousness necessarily exists when the prior

art range overlaps or touches a claimed range, such as in the instant rejection. MPEP § 2144.05. Regarding formoterol fumarate dihydrate, Applicants admit in paragraph [0006] that this salt hydrate of formoterol is well-known. Regarding claims 5-6, assuming a density of ~ 1 g/ml for the resulting prior art propellant formulation while in the MDI and a total volume of 100 mL, the concentration of formoterol would range from 0.025 mg/ml to 1 mg/ml (Oliver) and the concentration of mometasone would be 2.69 mg/mL (Gavin). Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed May 5, 2010 have been fully considered but they are not persuasive. Applicants have traversed the instant rejection by attacking the cited references individually and arguing that (1) the rejection is allegedly flawed because Cutie does not teach formoterol fumarate dihydrate and mometasone furoate alone or in combination, (2) Cutie is allegedly not enabled for any specific combination of drugs, (3) Cutie is deficient, because Cutie refers to sugars in MDI formulations as dispersants and not as "bulking agents" as these components are labeled by Applicants, and (4) no combination of the cited references would result in the combination of Cutie's dispersant as a bulking agent with a reasonable expectation of success.

The Examiner respectfully disagrees with Applicants' traversal arguments. In response to applicant's arguments (1)-(3) against the references individually, one cannot show

nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Regarding (4), Applicants argument represents mere argument absent any technical or scientific explanation as to why the ordinary skilled artisan would reasonably expect the combination of the cited references to be unsuccessful. Furthermore, the lable Cutie uses to refer to lactose is immaterial. Lactose is an art-recognized bulking agent. Reference by Cutie to lactose as a dispersing agent does not change this fact. Thus, Applicants'' arguments are unpersuasive. The instant rejection is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 5-14, and 17 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 39-61 of copending Application No. 12/472,088 (copending '088) in view of Gavin et al. (WO 01/78740).

Applicants' claims 1 and 17 have been described above. Independent claim 39 of copending '088 claims a pharmaceutical aerosol formulation comprising (i) particles of drug dispersed (i.e. suspended), (ii) propellant, and (iii) a bulking agent having a mass median diameter of less than one micron. Dependent claim 42 of copending '088 further specifies that the bulking agent is lactose. Dependent claim 39 of copending '088 specifies that the drug may be selected from a group including formoterol.

The primary difference between the claims of the instant application and the claims of copending '088 are that the claims of copending '088 (1) do not specifically recite the combination of formoterol and mometasone and (2) do not recite a dispenser having its interior surfaces coated with a fluorocarbon polymer. These deficiencies are cured by the teachings of Gavin and Ashurst, which are set forth above. Regarding the limitations of the other dependent claims of the instant application and copending g'088, these limitations are substantially similar in both applications. Regarding formoterol fumarate dihydrate, Applicants have admitted in paragraph [0006] of their specification that this salt-hydrate of formoterol is well-known in the prior art. Therefore, a person of ordinary skill in the art at the time of the instant invention would have found claims 1-14 and 17 *prima facie* obvious over claims 39-61 of copending '088.

This is a provisional obviousness-type double patenting rejection.

Response to Arguments

Applicant's arguments filed May 5, 2010 have been fully considered but they are not persuasive. Applicants' arguments did not traverse, and in fact, did not address the instant provisional obviousness-type double patenting rejection. The instant rejection is maintained.

Conclusion

Claims 1, 5-14 and 17 are rejected. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571)

272-5548. The examiner is on a flexible schedule, but can normally be reached on M-F ~10am~5:30 pm, and Saturdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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